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TITLE: Multimodal Intervention Trial for Cognitive Deficits in Neurofibromatosis Type 1: Efficacy of Computerized Cognitive Training and Stimulant Medication

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14. ABSTRACT During this research period, we successfully developed a plan for participant recruitment and human subjects approval, identified and trained study personnel, created research database, submitted for and obtained IRB approval for the coordinating site (Children's National), and enrolled 8 participants. Two participants completed the assigned condition and completed the final neuropsychological assessment.					
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1. INTRODUCTION: The purpose of this research is to assess the efficacy of a home-based, computerized cognitive training (CT) program in a sample of 90 children aged 8-16 with NF1 and working memory difficulties. Participants will be stratified by stimulant medication use and randomized equally between two computerized cognitive training interventions within stratum. Participants will be in the study for up to 11 weeks. Each participant will be assigned a computerized training coach who will work with them weekly via a telephone call to provide trouble-shooting, brainstorm strategies for maintaining motivation, and provide feedback on training progress to date. Improving working memory difficulties may help to offset problems with intellectual quotient, executive functioning, and academic performance in children with NF1 over time. Given the high incidence and burdens of attention and WM problems in children with NF1, identifying feasible and efficacious interventions is a critical priority.

2. KEYWORDS: neurofibromatosis, cognition, pediatric, computerized training programs, working memory

3. ACCOMPLISHMENTS:

What were the major goals of the project?

As stated in the approved SOW, the major goals of the project included 1) developing a plan for patient recruitment and human subjects approval (months 1-6); 2) identification and training of study personnel and database initial activities (months 2-6); 3) participant recruitment, therapy, and participant evaluation (months 1 until end of study), and 4) cleaning and analyzing data from patient recruitment, evaluations, safety data, and neuropsychological data, specifically reviewing data monthly for completeness and accuracy and resolving queries with sites (months 9 until end of study).

What was accomplished under these goals?

Our first major task was to develop a plan for patient recruitment and human subjects approval. We successfully refined study eligibility criteria, exclusion criteria, and study screening protocol; finalized the consent form and human subjects protocol; coordinated with sites to establish a regulatory binder; and coordinated with sites to submit to DoD to obtain approval of their site. We are actively coordinating with other sites regarding material transfer agreements or clinical trial agreements submission. We are also actively coordinating with the four other participating sites related to submitting the study for local IRB approval. Three sites have submitted the study to their local IRB and are waiting for study approval. This process has taken longer than expected, largely due to site IRB concerns of privacy and confidentiality related to using a technological intervention. Indeed, we have had to obtain a Certificate of Confidentiality for the study from the National Institutes of Health in order to assure IRB personnel at participating sites that the data collection and storage will be protected, and this has significantly increased the amount of time required for IRB submission and approval. We at Children's National, as the coordinating center, successfully submitted for IRB approval in February 2016 and received IRB approval May 10th, 2016.

- HRPO protocol application was submitted on June 2, 2016 and was approved on June 24, 2016.

- CHLA: IRB protocol submitted September 9, 2016
- Sydney: IRB protocol submitted September 6, 2016
- Westmead: IRB protocol submitted September 6, 2016
- Boston: currently developing IRB protocol

As for stated goals not met, we did not coordinate with sites regarding annual IRB continuing review as we are currently the only site open. As the other sites do not have IRB approval, it is not yet time for an annual continuing review.

Our second major task was the identification and training of study personnel and beginning database initial activities. With regards to the identification and training of study personnel, we coordinated with sites and successfully identified study personnel; coordinated with sites regarding psychologist/psychometrician training; designed data collection forms; designed database; conducted data collection validated and implementation tests; created a randomization schedule and randomization database; developed coaching record logs; and highlighted procedures for dealing with urgent or emergent clinical issues. Of note, the unexpected retirement of our lead statistician, who also managed the coordinating center staff, Dr. Avital Cnaan, led to additional turnover among the coordinating center staff who also worked on this protocol. As a result, we had numerous, and unanticipated, personnel changes at Children's National, particularly during Quarters 2 and 3. Because our core scientific team of Drs. Acosta and Hardy were consistent, however, this did not materially impact the progress of our work on the project. However, we have had to expend additional time training new staff as they have been onboarded. In addition, we made the decision to have a dedicated, full-time, doctoral-level Clinical Research Manager, Dr. Katie Olson, assume the duties that were originally dispersed among several study staff. Dr. Olson has previous research experience with Cogmed in medical populations, is a licensed psychologist, and has data management expertise, so she is able to manage multiple processes required in the coordinating center.

As for stated goals not met, we are prepared to coordinate with sites for Cogmed coach training and supervision of coaches once they receive IRB approval. We plan to provide coach training through having identified coaches complete Cogmed coach training, as well as providing support through interactive conference calls and answering questions via email. We as the coordinating site will be available to provide supervision of Cogmed coaching to problem-solve coaching issues and to refine coaching procedures consistently across sites.

Our third major task was participant recruitment, therapy, and participant evaluation. We at Children's National successfully enrolled 8 participants. We have conducted 8 baseline assessments and have had two participants successfully complete the computerized training intervention and return for follow-up assessment. While our goal for the end of the year was to recruit a total of 15 patients across 5 sites, we do not believe that the discrepancy between the proposed and actual enrollment to date will affect our ability to fully accrue our targeted number of participants. Specifically, we believe that we will quickly progress towards our target accrual once the other four sites receive IRB approval and begin enrolling participants. Additionally, accrual at Children's National has been faster than expected. We have

achieved 133% of our predicted enrollment over the last two quarters and have four additional enrollment visits scheduled in the next month.

The rest of the goals subsumed under the third major task are ongoing, including monitoring recruitment process, retention, and completion of the final assessment; monitoring regulatory compliance (IRB continuing approvals) and GCP compliance; complete follow-up assessments after Cogmed training is complete; and having monthly meetings with all sites to discuss progress and engage in troubleshooting.

Our fourth major task involved cleaning and analyzing data from patient recruitment, evaluations, safety data, and neuropsychological data. Since Children's National is currently the only site open and enrolling patients, we are the only site currently managing study data. Data from participants is entered into a database by appropriate team member, where data is reviewed for completeness and accuracy by database manager.

The rest of the goals subsumed under the fourth major task are either ongoing or to be performed at a later time. Those that are ongoing include reviewing data monthly for completeness and accuracy and resolving data queries with sites. Those that are to be performed at a later time include summarizing data after the first 30 and 60 participants; summarizing all data; performing all analyses per analysis plan; sharing findings with investigators; and disseminating findings through abstracts, presentations, publications and to the funder.

What opportunities for training and professional development has the project provided?

Nothing to report.

How were the results disseminated to communities of interest?

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?

During the next quarter, we plan to have the four other sites successfully submit for IRB approval, obtain IRB approval, and begin recruiting and enrolling subjects. Our goal is to enroll a total of 63 participants by the time of the next annual report, which will be accomplished by enrolling a total of 3 participants at each site over 4 quarters.

4. IMPACT

What was the impact on the development of the principle disciplines of the project?

As there is only one site currently enrolling study participants, it is too soon to have a sense of the impact of this study on the development of the principle disciplines of the project.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

5. CHANGES/PROBLEMS**Changes in approach and reasons for change**

We did not make any changes in the approach that was approved by the funding agency.

Actual or anticipated problems or delays and actions or plans to resolve them

1) In 2015, Cogmed phased out support for the non-adaptive training, which was previously the active control in this study. As detailed in the scientific rationale the company provided to justify this change, it was noted that, in early phases of evaluating the efficacy of Cogmed, non-adaptive training was a useful tool to test the hypothesis that in order for training to have an effect, an individual needs to train at a level that is constantly challenging his or her working memory. However, developments in the field have led to consideration of some of the limitations regarding the appropriateness of this non-adaptive training as a control for current research hypotheses. Specifically, there is now evidence that the non-adaptive training may actually serve as a “low dose” of working memory training for some groups rather than a clear control condition.

As evident by large training-related improvements for non-adaptive trainees with low-baseline working memory capacity (Dunning et al., 2013), young children with ADHD (van Dongen Boomsma), or persons with intellectual disabilities (Södersvist et al, 2012 Van der Molen, 2010), non-adaptive training may lead to a training effect. For these groups, holding even two or three items in mind may be a challenge to their existing capacity. Shipstead et al. (2012) stated that non-adaptive trainees may not be convinced that they are really engaged in cognitive training and do not receive the feedback of improvement imparted by increasing task difficulty that the adaptive group receives. Therefore, non-adaptive training will not be provided by Pearson for this research study, making us change our focus to a new active control.

Upon discovering that the non-adaptive version is no longer being offered, we conducted an in-depth search on alternative programs that could achieve a similar effect that did not change the research design. The most ideal option was a program called MobyMax.

MobyMax is an adaptive, online educational program that targets academic skills across a range of subject areas (e.g., reading fluency, reading comprehension, math computation, etc.). It is designed to be completed by children aged 5+ on a desktop or laptop computer or tablet device with minimal parental supervision. MobyMax’s “Reading Stories” program is an adaptive activity that mirrors Cogmed on a learning level. Each grade contains 30 lessons, in which each lesson contains 3 stories that are

tailored to the participant's grade level. They are given questions to answer at the conclusion of each story. Depending on whether the participant passes or fails, the adaptive program will place the participant at the appropriate reading level. Participants randomized to this program, will be asked to spend the same amount of time as the participants randomized to Cogmed (i.e., 30-45 minutes per session for 25 training sessions over a 5 to 9 week period), and there will be a coach that will access and track each participant's progress, as well as provide weekly, phone based coaching support.

Like Cogmed, MobyMax provides an adaptive, computerized, home-based program requiring minimal caregiver oversight. Participants randomized to either MobyMax or Cogmed will complete the same number of sessions, for the same amount of time, with the same level of phone-based coaching and the same availability of online tracking. Thus, the only difference between the treatment and control conditions is that Cogmed trains the construct of interest, working memory, whereas MobyMax is focused on reading. Indeed, in light of the evidence indicating that the nonadaptive version of Cogmed may actually improve working memory in some individuals, or be less engaging for others, we believe that MobyMax may be a better active control condition than our original selection because it does not train working memory, will be more engaging than the nonadaptive version of Cogmed, and is also a program clearly designed to be helpful to young learners.

In conclusion, due to these unforeseeable circumstances with the active control condition originally planned for the study, the submission of the Coordinating Center protocol to the IRB was significantly delayed

2) It has taken longer than we originally anticipated for other sites to obtain IRB approval. IRB analysts and reviewers have many questions regarding computerized cognitive training programs and have required lengthy documentation of explanations regarding protection of privacy and confidentiality. Three of the four sites have successfully submitted to their local IRB and supplied reviewers with requested information, so we anticipate that approval will be forthcoming shortly at those sites. One site remains in the stage of preparing to submit for IRB approval, and we are working with them to ensure that this is accomplished in a timely manner.

Changes that had a significant impact on expenditures

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

There were no significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period.

Significant changes in use or care of human subjects

There were no significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects.

Significant changes in use or care of vertebrate animals

Vertebrate animals are not used in this study.

Significant changes in use of biohazards and/or select agents

There were no significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of biohazards and/or select agents.

6. PRODUCTS

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Name:	Maria T. Acosta, M.D.
Project Role:	PI
Researcher Identifier:	ORCID ID 0000-0002-7645-0011
Nearest person month worked:	0.3 per quarter/1.2 per year, cost sharing support by CNMC for an additional 0.3 per quarter /1.2 per year
Contribution to project:	Overseen all details regarding all necessary documents to submit to DoD and IRB
Funding support:	
Name:	Kristina K. Hardy, Ph.D.
Project Role:	Co-PI, Site Investigator
Researcher Identifier:	ORCID ID 0000-0002-5479-5043
Nearest person month worked:	0.3 per quarter/1.2 per year, cost sharing support by CNMC as above
Contribution to project:	Overseeing neuropsychological assessments and intervention methods as outlined in protocol
Funding support:	
Name:	Avital Cnaan, Ph.D.
Project Role:	Lead Statistician
Researcher Identifier:	ORCID ID 0000-0002-0312-4792
Nearest person month worked:	0.24 per quarter/1 per year
Contribution to project:	Provided statistical expertise on protocol
Funding support:	
Name:	Marni Jacobs, Ph.D. (replaced Avital Cnaan)
Project Role:	Lead Statistician
Researcher Identifier:	ORCID ID 0000-0001-6649-6692
Nearest person month worked:	0.24 per quarter/1 per year
Contribution to project:	Provided statistical expertise on protocol
Funding support:	

Name	Lauren Morgenroth, MS
Project Role:	Operations Manager
Researcher Identifier:	ORCID ID 0000-0003-4140-3829
Nearest person month worked:	0.3 per quarter/1.2 per year
Contribution to project:	Supervised clinical research manager in protocol development and consent form creation
Funding support:	
Name:	Adrienne Arrieta, MS
Project Role:	Data Manager
Researcher Identifier:	N/A
Nearest person month worked:	0.15 per quarter/0.6 per year
Contribution to project:	Supervised data manager in CRF and EDC creation
Funding support:	
Name:	Lindsey Vacovsky, MPH
Project Role:	Clinical Research Manager
Researcher Identifier:	ORCID ID 0000-0002-0333-3084
Nearest person month worked:	0.75 per quarter/3 per year
Contribution to project:	Protocol development and Consent form template creation
Funding support:	
Name:	Maya Shimony, MPH
Project Role:	Data Coordinator
Researcher Identifier:	ORCID ID 0000-0002-0594-0371
Nearest person month worked:	0.75 per quarter/3 per year
Contribution to project:	CRF and EDC creation
Funding support:	
Name:	Ja Lee, MR
Project Role:	Study Coordinator
Researcher Identifier:	N/A
Nearest person month worked:	1.5 per quarter/6 per year via cost sharing support by CNMC
Contribution to project:	Facilitated communication between all sites
Funding support:	
Name:	Wenze Tang (replaced Maya Shimony)
Project Role:	Data Coordinator
Researcher Identifier:	N/A
Nearest person month worked:	0.75 per quarter/3 per year
Contribution to project:	CRF and EDC creation
Funding support:	

Name:	Katie Olson, PsyD (replaced Lindsay Vacovsky)
Project Role:	Clinical Research Manager
Researcher Identifier:	ORCID ID 000-0003-3695-6891
Nearest person month worked:	1.5 this quarter/6 per year
Contribution to project:	Facilitated communication between all sites, protocol refinement, coordination of study materials and operations.
Funding support:	

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report.

What other organizations were involved as partners?

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

None.

9. APPENDICES

None included.